

THE STRUCTURE OF MONOCROTALINE

BY

ROBERT SIDNEY LONG

B.S., St. Mary's College, 1936

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE UNIVERSITY
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THE STRUCTURE OF MONOCROTALINE

INTRODUCTION

Monocrotaline has been isolated from the seed of *Crotalaria spectabilis* and shown to have the empirical formula $C_{16}H_{23}O_6N$.¹ Alkaline hydrolysis gives retronecine, the base present in many *Senecio* alkaloids, and an acid, $C_7H_{12}O_3$, designated as monocrotic acid. Hydrogenolysis gives a base, retronecanol, and monocrotalic acid, $C_8H_{12}O_5$, the acid which is believed to be present esterified with retronecine in the alkaloid. It is the attempts to determine the structure of this acid by means of degradative and synthetic reactions that form the basis for this work.

THEORETICAL AND DISCUSSION OF RESULTS

Monocrotalic acid is monobasic but back titration of the acid from excess alkali indicates the presence of a lactone. It forms a crystalline monomethyl ester which was shown by a Zerewitinoff determination to contain one active hydrogen. This indicates that the fifth oxygen atom is present as a hydroxyl group but attempts to obtain hydroxyl derivatives were uniformly unsuccessful.

Treatment of monocrotalic acid with concentrated alkali effects a smooth and quantitative conversion to monocrotic acid. Since monocrotic acid was shown to be identical with α,β -dimethyllevulinic acid,² any structure predicted for the acid must be capable of such a transformation. Since levulinic acid is tautomeric with γ -hydroxy- γ -valerolactone,³ it was thought that a similar hydroxylactone group might be present in monocrotalic acid and would be stabilized by the additional substituents on the α - and β -carbon atoms. The position of the free carboxyl group must be such that decarboxylation in the presence of alkali may be explained.

On the basis of these observations, it appeared that monocrotalic acid must be α -carboxy- α,β -dimethyl- γ -hydroxy- γ -valerolactone (I), β -carboxy- α,β -dimethyl- γ -hydroxy- γ -valerolactone (II), or δ -carboxy- α,β -dimethyl- γ -hydroxy- γ -valerolactone (III). Structure III seemed unlikely, however, since it contains a primary carboxyl group which should esterify easily, whereas monocrotalic acid can be esterified satisfactorily only with diazomethane. If compound II is correct, methyl anhydromonocrotalate would contain a terminal methylene group but such a group could not be detected.

In an attempt to confirm structure I, ethyl α -carbethoxy- α,β -dimethyllevulinate was synthesized from methyl α -bromoethyl ketone and diethyl malonate followed by methylation with methyl iodide. Since this ester did not decarboxylate during alkaline saponification it seems improbable that monocrotalic acid corresponds to compound I. Decarboxylation of the oily acid obtained by saponification gave α,β -dimethyllevulinic acid which was shown to be identical with monocrotic acid by comparison of the dinitrophenylhydrazones of the methyl esters.

Ethyl β -carbethoxy- α,β -dimethyllevulinate was, therefore, synthesized from ethyl α -bromopropionate and ethyl acetoacetate followed by methylation with methyl iodide. This compound lost carbon dioxide during alkaline saponification. The α,β -dimethyllevulinic acid obtained was shown to be identical with monocrotic acid. This is a strong indication that monocrotalic acid possesses a configuration such that a β -keto acid is formed in the presence of alkali. Hydrolysis by refluxing with concentrated hydrochloric acid gave α,β -dimethyllevulinic acid and hydrolysis at room temperature gave β -carbethoxy- α,β -dimethyllevulinic acid (IV).

Neither compound IV nor crude α -carboxy- α,β -dimethyllevulinic acid showed any tendency toward hydroxylactone formation. This indicates that such a configuration may not be present in monocrotalic acid but a satisfactory alternative structure is not available at present.

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² Adams, Rogers and Sprules, J. Am. Chem. Soc., **61**, 2819 (1939).

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VITA

The writer was born in Chicago, Illinois, on March 30, 1916. He received his elementary education in the public schools of Winona, Minnesota, and Chadron, Nebraska, and was graduated from the former school in June, 1932. Upon graduation he received a scholarship at St. Mary's College, Winona, which he held until June, 1936, when he received the degree of Bachelor of Science. He attended the University of Minnesota Graduate School during the year 1936-1937 and held a teaching assistantship in the University of Illinois during the years 1937-1940.

